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EDITORIAL

HEAVY HORSES

THE heavy horses of Britain, once the pride of the countryside and faithful slaves on the farms and roads, have come to fateful days. The urge for speed, the shortage of suitable manpower, and high wages are responsible for their decline in numbers and from favour. Probably the main factor for the dethronement from their erstwhile high estate is the want of suitable manpower. A modern young man does not set high value on any job which entails that he may be required to work beyond regulation hours, and especially so if it impinges upon the week-end. An automobile suits this inert mood. It is devoid of sense, feeling, or intelligence and offers no rebuke to its driver's conscience on being deserted at close of day.

In spite of these difficulties the Breed Societies and many breeders and owners have remained faithful to their horses and continued to do a fine job. Conformation, quality, action and even temperament have been improved by selective breeding designed to meet the requirements of the commercial user and tuned towards perfection by the judges in the showring. For many years, the State, recognising the value of the horse in the national economy, has given encouragement and financial assistance to the various breed societies so that selected sires could be available in all areas and at a price that would be within the measure of the smallest farmer's pocket.

This policy has paid great dividends and the quality of the animals which have been available to the commercial user in recent years bears striking witness

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to the wisdom of the scheme. There can be little doubt that, if the internal combustion engine had not made such great inroad into the realm of traction during the last few decades, the quality of the ordinary working horse would have equalled even that of the best specimens on show today.

We regret the withdrawal of official support and especially so because it has been withdrawn at such a critical time in the affairs of the working horse. Our horses are a sacred heritage which we should treasure and nurture in good times and in bad and it is the acme of parsimony, ingratitude and want of vision to deny them their mite from the National Exchequer. The heavy horses may be undergoing an eclipse, but this must not be allowed to become complete, for the time may come—it has been perilously near in recent months—when we may be in dire need of their help. The Breed Societies should be encouraged and helped in every way possible in their fight to preserve and improve the magnificent animals and safeguard them for the future. Quantity is not the sole criterion of value. Quality is the essential factor. In this latter respect the culling which has taken place may be to the advantage of the various breeds.

In a restricted market the buyer calls the tune and there is no place for second-class goods. When the market is bounding and the vendor is supreme, inferior material can find a ready sale. The prosperity of the horse-breeding industry is reflected in the demand for good-quality geldings, and the measure of this demand is the purchase price achieved at public auction. The best geldings still fetch high prices, competition is keen, and even in a limited market the supply is not equal to the demand. It is obvious that the stoppage of State financial assistance may have a serious effect upon the number of stallions available in the country and breeding will decline further. Horses have served us well in the past, their role may be limited at the present time, but they may be vital to our existence in a future in which a few men can bring all mechanically-propelled wheels to a sudden halt.

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GENERAL ARTICLES

A CRITICAL APPROACH TO CANINE VIRUS DISTEMPER

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Introduction

THIS article is an attempt to provoke a critical discussion on the state of our present knowledge of canine distemper. It is not a complete review of literature on modern virological trends or on canine virus distemper. Facts and speculations regarding canine virus distemper have come from many diverse sources and have been expressed in many reviews. This paper concerns itself primarily with a limited number of problems of practical as well as theoretical importance which still await complete solution. Only selected publications will be reviewed with the intention of emphasising the significance of unsolved problems. Four matters of practical importance will be considered, namely: (a) the complexity of Laidlaw and Dunkin's virus and some associated problems, (b) the pathogenesis of distemper, (c) " classical " distemper, " hard pad " and " paradistemper," and (d) prevention of the disease. Further progress in our knowledge of canine virus distemper must depend upon the recognition of these unsolved problems and the vigour with which they are investigated.

What is Canine Distemper?

A historical review of the virus diseases with characteristic and easily recognisable symptoms, lesions and epidemiology, such as the poxes and rabies, might justifiably lead to the conclusion that these diseases have existed a very long time and have changed little in character. A similar examination of the known facts concerning canine virus distemper would not lead to such a definite conclusion since canine distemper virus produces in the dog neither characteristic signs nor lesions. It seems probable that there were and still are many different infections which give rise to fever, coryza, pneumonia and nervous disorders in affected dogs. For instance, it is only during the last eight years that canine virus hepatitis has been differentiated from virus distemper. This is in itself proof that the word " distemper," even when used professionally, was and very probably still is used as a name to cover more than one specific disease of the dog.

It was not until 1905 that Carré suggested that a virus was the causative agent of canine distemper. Although Carré never transmitted the virus to experimental animals, nor proved experimentally that the signs and lesions in the dog attributed by him to virus activities were produced by a single virus entity, nevertheless our present knowledge of the viral nature of distemper began with his discovery.

Laidlaw and Dunkin (1926) were the first to isolate in the ferret a virus originating from dogs affected with distemper. These authors were also the first to passage the virus in ferrets and dogs and to describe some of its properties and the lesions it caused. For this reason, canine distemper virus is sometimes called

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Laidlaw and Dunkin's virus, and the illness it causes, Laidlaw and Dunkin's disease.

Since Laidlaw and Dunkin's (1926) description of the virus it has generally been accepted that distemper virus is a single entity which produces in the dog and in the ferret an acute disease with remarkably constant pathogenesis, essentially the same in both species. In 1948, Holmes attempted to classify this virus with the other animal viruses into species, genera and families, and to give them internationally recognised names. Canine distemper virus received the name *Tarpeia canis,* and undue emphasis was laid upon certain of its general characteristics implying extreme simplicity of structure and an inability to undergo a transformation. Subsequent research has gradually shown that neither the virus nor all clinical forms of the disease quite fit the descriptions given by Laidlaw and Dunkin. A tendency has consequently developed to give new names to different types of Laidlaw and Dunkin's virus and to different forms of the disease (" hard pad," " paradistemper "), as if the latter were caused by entirely unrelated virus entities.

There is some point in using a non-specific term such as " The Distemper Complex " for canine distemper. Unfortunately, however, it is now used loosely to cover not only modifications of this virus disease but also to include those diseases of the dog in any way simulating clinically the disease caused by the distemper (Laidlaw and Dunkin) virus. Thus in their book " The Distemper Complex " by Whitney and Whitney (1953), the authors include such diseases as Carré's disease, hard pad, infectious hepatitis, coccidiosis, toxoplasmosis and leptospirosis. Clearly, in introducing new terminology, care must be taken to ensure that it is helpful to progress and is not creating an unwanted confusion.

Recent studies of 55 strains of virus isolated from outbreaks of distemper in various parts of Britain have revealed the complexity and diversity of the distemper virus (Larin, 1955). These studies have shown that canine distemper is not caused by a homogenous virus but by one which can exist in several types (A, B and C), and these are not stable entities with predictable behaviour. These variants may undergo changes and are able to give rise to new forms of a modified nature and of a different biological behaviour. The plurality of virus types may itself cause variations in the disease.

These and other findings force a re-examination of the fundamental knowledge on canine distemper virus reported over the last 30 years, including the pioneer work of Laidlaw and Dunkin.

Outstanding Problems of the Laidlaw and Dunkin's Complex Virus

We propose to review only a few outstanding problems of the Laidlaw and Dunkin's complex virus, namely infectivity, genetic interrelations, toxicity, antigenicity and association of the virus particles with components of infected cells.

Infectivity.

The study of virus development is hampered by the fact that viruses cannot be grown in a cell free artificial medium. The word " isolation " has a different

meaning when applied to animal viruses from that understood when applied to bacteria, since animal viruses have not been completely isolated from components of host tissues. Our powers of recognition of viruses are limited as the size of virus particles is below the limit of the resolution of the optical microscope, and, further, they can only multiply inside specific living cells. Indeed, we fail to detect multiplication of a virus unless it is also capable of producing some detectable abnormality in the cells of its host.

At present the development and multiplication of animal viruses can be studied in association with multicellular populations only and not in a single infected cell. Furthermore, the detection of the presence of virus gives no hint of the number of cells that are infected nor to the manner in which they have acquired infection. Those viruses which are able to destroy specific cells are described as pathogenic. It is believed that this destructive ability is often acquired as a result of "adaptation," but this does not mean that an "unadapted" virus may not be able to multiply in the same cells. Clearly multiplication may occur without destruction.

Little is known about the way in which the interaction between virus and cell resolves itself in situations where the cell is not destroyed. Indirect evidence suggests that some viruses produce dormant or "latent" infection. The work of Shope (1943) on the latent swine influenza virus in lung worms suggests the existence of the virus in non-infectious form, but the nature of "activation" of latent viruses is still uncertain. It is also not clear whether infected cells can convey the dormant virus ("provirus") to their daughter cells; in other words, whether a "provirus" can be acquired without exogenous infection.

The process of multiplication by virus particles upon entry into cells has been studied in some detail with certain animal viruses and the results obtained have, in some measure, elucidated the mechanism of infection with the viruses concerned. The mechanism of infection with Laidlaw and Dunkin's virus (which has since proved to be more complex than they realised) and also the process of virus multiplication have not been investigated, and we are ignorant of the ways in which the virus functions in the body. This might be thought to be a theoretical problem and of no practical significance, but exact knowledge would dispel many suppositions and have valuable applications.

Since the developmental stages of Laidlaw and Dunkin's virus are not known, many hypotheses have been advanced concerning the mechanism of infection with canine distemper. For instance, it is generally believed that dogs kept on "infected" premises are necessary "exposed" to virus and will sooner or later acquire the infection and thereby develop an immunity. This does not happen always. To draw on our own experience, during the last two years we have received from many parts of Britain a number of adult dogs whose immunity to distemper has been challenged on arrival at our laboratory by inoculations of type A virus. It was found that the majority of these dogs did not resist the challenge and therefore were not immune to type A of Laidlaw and Dunkin's virus. By contrast, some young dogs which were born and reared in our isolated breeding kennels and had never, to our knowledge, been "exposed" to Laidlaw

and Dunkin's complex virus nor to the disease, were found to be immune to inoculation with 100 I.D. of the type A virus, although the majority of the dogs kept alongside them were not immune and developed the disease on virus inoculation.

Similar variations in susceptibility to infection were noticed in ferrets born and reared on "infected" premises. Female ferrets which had recovered from the illness produced experimentally with type C Laidlaw and Dunkin's complex virus, appeared to be immune when challenged with 100 I.D. of type A virus. Their progeny, however, born and reared on the "infected" premises and in "infected" cages, behaved differently. While some of the young ferrets acquired natural infection with Laidlaw and Dunkin's virus type A and died, the majority of the young ferrets escaped the infection even though, for a period of 18 months, they were susceptible to an inoculation of type A virus.

Our present knowledge of the mechanism of infection with Laidlaw and Dunkin's complex virus does not permit of any simple explanation of these facts. It is not enough to postulate variations in exposure and in resistance to viruses by individual animals.

Genetic Interactions.

In the case of the Berry-Dedrick phenomenon, it has been shown (Smith, 1952) that a heated extract of rabbit myxoma virus mixed with rabbit fibroma virus will "transform" the latter into myxoma virus. Burnet (1951 *a, b, c,* and 1953) and also Appleby (1952) reported upon an exchange of strain characters between type A strains of influenza virus. These results were interpreted by Burnet, Frazer and Lind (1953) as evidence of genetic recombination between virus strains.

The study of 55 strains of Laidlaw and Dunkin's virus (Larin, 1954 and 1955), isolated from different parts of Britain, showed that Laidlaw and Dunkin's disease is not caused by a homogenous virus. It is complex and comprises several virus types which undergo changes and are able to give rise to new forms of a modified nature and of a different biological behaviour. Nothing is known about the possible "genetic" and "non-genetic" material in this complex virus. Therefore it is not justifiable to speak of virus "mutations" and virus "mutants."

Toxicity.

Within recent years it has been proved that toxic substances are associated with certain viruses; the "endotoxins" of the lymphogranuloma venereum-meningopneumonitis group of viruses can be separated from the virus particles (Rake and Jones, 1944).

May not the toxic appearance of dogs during the acute phase in some clinical forms of Laidlaw and Dunkin's disease arise from some such viral toxin? This question is at present unanswerable since the possible toxicity of Laidlaw and Dunkin's complex virus has not been investigated.

Antigenicity.

The natural occurrence of antigenic materials, not necessarily associated with the infectious virus particles, seems to be a feature of almost all animal virus

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infections, including canine viruses. In the case of canine hepatitis virus, for instance, it has been established that antigenic activity of this virus *in vitro* is due to organised particles estimated to measure between 70 mμ and 105 mμ, although they may form larger aggregates. The chemical properties of these particles are those of protein, probably ribonucleoprotein (Larin and Orbell, 1956).

During the past two decades a wealth of information concerning various virus antigens, their nature and properties has been accumulated, and antigenic differences between virus strains have been measured. The possible detection of antigenic changes of viruses in relation to the epidemiology of virus diseases and immunity is important and would be significant.

What antigens are possessed by Laidlaw and Dunkin's complex virus and whether or not the complement fixing antigen of this virus is associated with the virus particle are questions which remain unanswered.

Association of Virus Activity with Components of Infected Cells.

A greater knowledge of the association of virus activity with various components of infected cells may provide an additional key to virus development. This approach, based on microscopy or on cytological techniques recently reviewed by Schneider and Hogeboom (1951), has been applied to a variety of virus-host complexes. Studies by Francis and Kurtz (1950), for instance, on herpes complex suggest that the intranuclear inclusion bodies seen in infected cells are not associated with virus particles. Ackerman and Kurtz (1952) have presented evidence which is interpreted as revealing close association of herpes virus with cell mitochondria. They found approximately 80 per cent of the virus " free " in the cytoplasm and about 10 per cent intimately tied to mitochondria. They assume that virus multiplication takes place in association with the latter, the virus being released into the cytoplasm after disintegration of the mitochondria. Similar suggestions may be inferred from work on rabies-infected mouse brain (Habel, *et al.*, 1952). The relation of poliomyelitis and of mouse encephalomyelitis viruses to cellular constituents has been investigated by a number of authors. Coffin, Coons and Cabasso ((1953) investigated, by means of fluorescent antibody, the relationship of canine hepatitis virus to the nuclear mass. Larin and Orbell (1955) similarly reported on the relationship between intranuclear inclusion bodies in canine virus hepatitis and the virus antigen.

Nothing is known of the association, if any, of Laidlaw and Dunkin's complex virus with various components of infected cells. The inclusion bodies often seen in lesions in Laidlaw and Dunkin's disease are no less enigmatic today than they were 30 years ago.

Pathogenesis of Distemper

Before a new form of disease caused by Laidlaw and Dunkin's complex virus can be accepted at least two conditions must be satisfied. It must be proved that a strain of Laidlaw and Dunkin's complex virus was present. The observed signs and lesions must be shown to be produced by this virus entity

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alone, and not by any combination of this virus with any other infectious agent which might be present in active or latent form in the dog. Before making a claim that a new form of Laidlaw and Dunkin's disease is being observed, its course of development must be studied from inception to the appearance of the characteristic lesions or signs. It must be shown that the new pathogenesis is entirely different from other known patterns of pathogenesis of the disease. If these criteria are applied it will be appreciated that many unjustifiable claims have been made for the existence of disease entities attributed to Laidlaw and Dunkin's complex virus.

In mouse pox, which it is believed is a valid model for the pathogenesis of the acute virus exanthems, quantitative studies of the virus titre in different organs and tissues of infected mice show that there is a regular stepwise progress of virus from the portal of entry through the regional lymphnodes to the blood stream, whence it is removed presumably by the macrophages of the liver and spleen. Multiplication occurs in these organs and the virus is released again into the blood stream in large amounts. Focal infection of the skin and occasionally of other organs follow the second viræmia and after a further period of multiplication, the virus concentration of the skin reaches a high level and lesions of the skin appear (Fenner, 1950).

In poliomyelitis there are various lines of evidence indicating the ways in which the virus and the susceptible nerve cell interact with one another (Howe, 1950), thereby providing an explanation of the different manifestations of the disease.

In influenza of man, viræmia in influenza being not considered an essential part of the pathogenesis, it would appear that the virus enters the body through the air and attacks the mucous membranes of the respiratory system, probably right from the nose down to the finest bronchioles (Andrewes, 1950).

What is the position with regard to Laidlaw and Dunkin's disease? What part does viræmia play in the pathogenesis of the disease? Do we know why the skin lesions appear only in some cases of the disease? Why does pneumonia occur only in some cases, while in others different lesions are observed? In what way or ways do Laidlaw and Dunkin's virus and the susceptible nerve cell interact?

It has been established at these laboratories that the type A Laidlaw and Dunkin's complex virus (Larin, 1955) can, after inoculation, be isolated from the cerebrospinal fluid on the first day of high fever (Larin and Singleton, 1955, unpublished observations). Can one diagnose encephalitis in the dog clinically as early as that? Do we know the pathogenesis of any form of Laidlaw and Dunkin's disease in sufficient detail to appreciate the sequence of events from inception of infection to the appearance of a specific lesion? Laidlaw and Dunkin (1926-1931), in their description of signs and lesions of the disease, did not make such a claim and neither has any subsequent author.

Reviewing our present knowledge it appears certain from examination of lesions caused by Laidlaw and Dunkin's virus that the virus has an affinity for several different specialised tissues, including the nervous tissue. Furthermore,

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it appears that the various tissues which may become involved are not necessarily attacked in any definite sequence as disease progresses. These facts explain the difficulties met with in attempts to establish a diagnosis on post-mortem findings, and also emphasise the great variety of tissue damage which can be evoked by this virus. With such diversity it is at present impossible to define which set of lesions is characteristic for the "classical" form of the disease, and which lesions are significant for the other forms. Much work must be done before we can elucidate the pathogenesis of Laidlaw and Dunkin's disease.

"Classical" Distemper, "Hard Pad" Disease and "Paradistemper"

A specific infectious disease is generally accepted to mean an illness which is induced by a specific agent, entirely separate from other infectious agents.

The acceptance of this definition prevents the confusion which would arise from a study of diseases of similar pattern but induced by different œtiological agents. Were it not for a rigid definition, a disease such as tuberculosis might have been separated into several "separate" entities, according to the pathogenesis of the different forms or to the types of the infectious agent. A similar approach to influenza of man would probably produce even more "new" diseases than in the case of tuberculosis. Whilst additions to detailed knowledge are always valuable, unjustifiable classification into separate compartments may mislead; indeed, it is probable that had this course been followed in the cases of tuberculosis and influenza, much less progress in our knowledge would have been made.

In the case of canine virus distemper the suggested division into "classical" distemper and "hard pad" disease (or "paradistemper") may lead to confusion rather than to clarification. The name "hard pad" disease originated from the studies of MacIntyre, Trevan and Montgomerie (1948). They actually described very carefully the lesions they observed in cases of canine encephalitis. They went further, however, and described in addition an illness which they considered to be a separate entity and which they called "hard pad" disease. The evidence for this conclusion is not convincing because MacIntyre, Trevan and Montgomerie (1948) stated in their paper (*a*) that the virus isolated from case of "hard pad" disease was related to the Laidlaw and Dunkin complex virus, (*b*) that efforts to reproduce "hard pad" disease experimentally failed, and (*c*) that it was suspected that the administration of sulphonamide drugs and probably also some factors other than virus were responsible for the development of "hard pad" disease in the field.

This evidence alone would appear to be sufficient to raise serious doubts whether either "hard pad" virus or "hard pad" disease exists as a separate entity. Further investigations into "hard pad" virus and "hard pad" disease subsequently conducted by many workers in different countries over a period of seven years have failed to produce evidence in support of the existence of "hard pad" virus or "hard pad" disease as separate entities. On the other hand it has been shown that there are differences in antigenicity and in biological behaviour of various strains of the Laidlaw and Dunkin complex virus in the

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ferret and that these depend on the complexity of the virus particle and on the existence of different types of this virus (Larin, 1955).

It is doubtful whether the use of the names "hard pad" virus and "hard pad" disease is desirable. One might as well try to make two different diseases from the icteric and non-icteric forms of canine virus hepatitis. It is essential to accumulate far more facts relating to Laidlaw and Dunkin's complex virus and to the possible differences in patterns of the pathogenesis of the disease.

Prevention of the Disease

The prevention of Laidlaw and Dunkin's disease is made more difficult by the following conditions:—

1. The disease is not notifiable and hence no reliable epidemiological data are available.

2. Accurate diagnosis by clinical signs and post-mortem findings is difficult; laboratory diagnosis is expensive and usually retrospective.

3. Quarantine rules and regulations are lacking except for the shows.

4. There is no control on the use of live virus for active immunisation. The virus being a commercial preparation is sold freely to veterinary surgeons and its use is not accompanied by any quarantine regulations.

5. No statistical information is available concerning the results of the use in the field of various sera and vaccines; their preventive value is estimated from general impressions rather than sound information.

As it is our intention to discuss the foundation of our knowledge on the specific prevention of the disease rather than to speak generally on preventive measures, we shall concentrate on passive and active immunisation against Laidlaw and Dunkin's disease. As with other virus diseases, the mechanism of acquired resistance in this disease seems to depend upon (*a*) the presence of protective antibodies or (*b*) the modification of susceptible cells through some initial experience with virus so that they are able to deal effectively with subsequent attacks of the virus or (*c*) a combination of both factors.

There is scope for much more work before our knowledge on the mechanism of immunity production is precise.

Passive Transfer of Immunity.

Specifically acquired immunity appears to be associated with the spectacular appearance in the body of humoral antibodies. These antibodies need not necessarily play a major part in the production of immunity since in most instances such a relationship has not been established. Nevertheless, it is a fact that antibodies appear regularly during the course of a disease probably as a physiological response of the body to foreign substances. Hence, quite apart from their possible role in immunity, antibodies are the object of a great deal of interest in their own right. For instance, their high degree of specificity when reacting with substances *in vitro* makes them valuable tools for the recognition of viruses and bacteria. Usually these reactions are accepted as being directly associated

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with immunity but there is no real proof of this. We can only be certain that this assumption derives from the study of a mechanism which *may* also play a role in immunity. It is true that, as a consequence of long pre-occupation with serum antibodies, a tendency has developed to confine the entire field of immunity within the bounds of the activity of antibodies. This restriction of thought has limited experimental exploration for many years.

If we turn to a consideration of the circumstances under which immunity to Laidlaw and Dunkin's disease is revealed from the passive transfer of the antiserum we find that passively immunised dogs will generally resist the virus inoculated subcutaneously. This administration of virus is, of course, an artificial one and is usually associated with some trauma at the site of inoculation, no doubt leading to the passage of antibodies from the blood into the area of injection. This is, in fact, what Morgan (1949) found in animals inoculated with poliomyelitic virus. It is not known whether Laidlaw and Dunkin's complex virus is similarly subject to the activity of antibodies in spontaneous infection, or whether some circumstances under which a spontaneous infection may occur can account for a success or failure in passive immunisation.

We may ask what is the protective antibody itself, and how can one determine accurately the protective value of antiserum? It is known that the influenza virus incites the production of probably three distinct antibodies. Do we know how many antibodies can be incited by Laidlaw and Dunkin's complex virus? Do we know why a low concentration of the virus-neutralising antibody in the antiserum does not necessarily mean that the protective value of this serum is lower than that of a serum with a high titre of the neutralising antibody? It is not yet possible to answer these questions in the affirmative.

It is known that batches of antiserum against Laidlaw and Dunkin's complex virus may vary considerably in their potency, and there have been a number of interesting speculations and some experimental observations concerning this matter. Since the mode of action of serum antibody or antibodies upon the virus is not clear, the protective value of antisera is estimated by determining what modification, if any, is induced in experimentally produced Laidlaw and Dunkin's disease when antiserum is given. This test, though important, cannot be accepted as giving a true measure of the protective value of antiserum (Laidlaw and Dunkin, 1931). A useful foundation for further work on the problem of passive immunity is provided by the knowledge that the protective antibody or antibodies against Laidlaw and Dunkin's disease are associated with the gamma-globulin fraction of antiserum (Larin and Hodgman, 1955).

Active Immunisation.

Unfortunately, there are no statistical data available by which the preventive value of different methods of active immunisation can be compared. There is fairly convincing evidence that active immunity against Laidlaw and Dunkin's disease can be induced by the use of several different methods. It is extremely interesting to find that some dogs subjected to the process of active immunisation may appear for some unknown reason to be non-immune.

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There are two basic weaknesses inherent in the immunising procedures available at present. The first is associated with virus variation because canine distemper virus strains undergo change fairly readily (Larin, 1955). This indicates that it is unlikely that a vaccine prepared from a single strain will protect against the different types of Laidlaw and Dunkin's virus operating in the field. The effect of virus variation on the problem of vaccination has been illustrated by the example of the influenza virus. Against human influenza it was statistically shown that a polyvalent influenza vaccine consisting of "A" and "B" type viruses was highly effective in reducing human influenza morbidity during the 1943-44 "A" and 1945-46 "B" epidemics. In 1947, however, the vaccine was completely ineffective and the failure was shown to be the result of the marked difference between the "A" components of the vaccine and the variant "A1" strains which caused the epidemic (Hilleman, 1954). In the light of these data it is important that we should know much more about the antigenic characteristics of current virus strains which cause sporadic or epidemic outbreaks of Laidlaw and Dunkin's disease if we are to control them effectively.

The second basic weakness in the present active immunising procedure is that we know nothing about the actual immunity inducing factors in the Laidlaw and Dunkin's virus. That is to say that we do not know what constituent of the virus elementary body does, in fact, involve immunity. Bearing in mind that virus "cultures" are really suspensions of infected tissues containing an unknown number of virus particles of an unknown antigenic make-up, it is obviously important to possess the knowledge which will enable us to detect antigenic differences not only between two strains of the virus but also between different "cultures" of one virus strain.

As we are ignorant of the identity of the immunising factor or factors of Laidlaw and Dunkin's complex virus, we cannot discuss its relationship to the virulence of the virus. We know nothing either about the mechanism determining the virulence of the virus. We have insufficient experimental evidence to form even a tentative deduction as to what is the major factor in the body which is responsible for the state of active immunity, the functioning of neither antibodies nor cells in their protective capacities being fully understood.

Specific Treatment

Owing to the variety of tissues, physiological systems, and organs which can be affected directly by Laidlaw and Dunkin's complex virus and to the fact that virus-infected cells and tissues seem to provide suitable soil for the proliferation of various bacteria, the disease may show a variety of clinical features. For these reasons it is difficult to accept any chemical substance as a cure for "old-time distemper" or "hard pad" or both.

It seems reasonable to assume that the mechanism of virus activities within infected tissue cells will be related to the physico-chemical configuration of the active centres of the virus particle and their interaction with those of the infected cell. These interactions will vary with the particular structure of the invading

virus particles, their number, and with the particular structure of the invaded cell (cells for the nervous tissue, for instance, differ considerably in their structure from cells of the lungs). Quastel and Wooldridge pointed out in 1928 how accessibility and subsequent activity could vary greatly with both the chemical structure of a substrate and the physico-chemical structure of the active centres of living cells. It is conceivable that viruses are only activated when they are in living cells because they become associated with active centres within the cell. When activated in one cell a virus may exhibit somewhat different properties from its counterpart activity in the cell of another type of tissue as the change induced in the activated molecule may be different. It may be, therefore, that a single substance will not be able to interfere with the activated virus as found in cells of different types. Whilst a substance may "react" with an activated virus in, for example, lung cells, and so have a curative effect when used in the treatment of pneumonia, the same substance may be unable to affect that same virus when activated in a different type of cell, e.g., brain cells. The substance may then have no curative effect if used in the treatment of encephalitis caused by this virus.

Specific treatment may require different chemotherapeutical substances depending upon whether the virus-infected cells are part of the nervous, the lung or some other system. If this proves to be so then careful clinical diagnosis of the nature of a distemper attack will be essential to rational treatment.

Whilst such a specific treatment is still awaited it is feared that many cases of Laidlaw and Dunkin's disease are diagnosed as "incurable" largely because of economic reasons when many of them could probably be saved. In our experience many dogs with complicated Laidlaw and Dunkin's disease have recovered. Treatment consisted simply in the use of active antibody in the form of gamma-globulin in combination with the usual antibiotics in doses sufficient to suppress bacterial complications. Treated animals also received reasonable nursing.

Conclusions

A review of certain aspects of our present knowledge of canine distemper indicates that much more information must be acquired before the disease in all its variations can be brought under control. Some of the problems about which further information is required are the following:—

1. The nature of the distemper virus and its plurality.

2. The variability of virus types. The part played by adaptability to environmental conditions, mutations and genetic interactions.

3. Viral infectivity, virulence and antigenicity.

4. The pathogenesis of the disease, immunity response and specific treatment.

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THE PROBLEM OF THE TUBERCULOUS MONKEY

Some Observations on the Treatment of Tuberculous Monkeys

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Introduction

TUBERCULOSIS is a scourge of Primates—including mankind. Experience with lower Primates can contribute to the alleviation of human suffering, and vice versa.

An outbreak of tuberculosis occurred in a Monkey House. Seventy-three animals were affected. The administration of large doses of I.N.H. and P.A.S., and the institution of an open-air regime led to the return to health of more than half of the animals. When this result is compared with the general belief that a monkey infected with tuberculosis invariably dies of the disease within six months, the experience may be of some importance. The large dose of I.N.H. and P.A.S. employed may be of interest to those concerned with the disease in humans. Parallel with this clinical work, experience of tuberculin testing has thrown doubt on the belief that the tests hitherto described are reliable for all species, and the efforts made to overcome this difficulty and to institute a controlled routine of preventive vaccination will be described.

The Treatment of Clinical Tuberculosis in Primates

The Environment.

The long axis of the Monkey House of the London Zoo runs from N.W. to S.E. It is approximately 160 ft. long and there are cages on either side. The cages are separated from each other and the public by single chain-link fencing. On the north side of the house there are 17 inside dens, and on the south side 16. These inside dens communicate with an outdoor exercising den via a steel slide which is hand-operated from inside the house. A draught-preventing rubber flap is suspended over the exit when the steel slide is up in order to prevent excessive heat loss, and to allow the monkey free passage in and out as he wishes. At the north-west end of the south side of the house there are seven special ape dens for chimpanzees, orangs, etc., which are separated from the public by a large glass screen. All the other cages have crush-barriers at some 2 ft. 6 in. distance from them to prevent the direct access of public. This barrier does not stop people from feeding the monkeys. The outside dens are constructed of chain-link fencing so that the animals are able to get in direct contact one with the other, and in spite of crush-barriers, which are some 3 ft. from the cages, the public are able to feed the animals.

The Outbreak of the Disease.

The outbreak started in April, 1954, when there was a sudden incidence of deaths from tuberculosis. It is well known that most exhibitors of primates

expect the occasional death from tuberculosis. This fits in with the view, commonly expressed, that sub-human primates have no resistance, either natural or acquired, to tuberculosis. Up to the present time our monkeys have been constantly exposed to infection from the public. It is hoped that this will be remedied in any new Monkey House that is built. When the number of deaths increased significantly and rather suddenly it became apparent that an epidemic was starting. It is interesting to consider the reasons for this epidemic.

(*a*) The weather over the previous six months had been for the most part mild. This did not allow the monkeys a proper toughening-up period such as is usually experienced in the cold weather.

(*b*) There was a savage three weeks freeze-up in February which caused a few deaths. This intense cold period undoubtedly weakened many of the monkeys.

(*c*) Temperature control was extremely difficult to achieve.

(*d*) Cross infection cannot be controlled.

(*e*) Direct infection from the public feeding and spitting at the monkeys is a constant and as yet uncontrolled menace.

(*f*) Fluctuations in the quality of food in the early months of the year are unavoidable and may have an effect on the resistance of individual monkeys.

A graph was kept which plotted notified cases against date in order to assess the progress of the outbreak. This graph indicated a peak in late June. It fell rapidly through July to normal, when the outbreak as such was considered to be at an end.

Precautions Taken.

Once the outbreak occurred it was essential to take measures for the protection of the public, the staff, and the animals.

1. *The Public.* Owing to the possible but slight risk of human infection, the public were not admitted to the Monkey House during the outbreak. Animals obviously ill were presumed to be affected. They were removed immediately to the Sanatorium.

2. *The Staff.* (*a*) In the Monkey House. All staff were instructed to wear face masks while on duty in the house. Personal hygiene was rigidly enforced and chest X-rays organised. Arrangements were made for all staff to be Mantoux tested; those giving negative results were offered B.C.G. vaccination. No non-reactor was allowed to continue working in the house if he was unwilling to be vaccinated. There were no cases of tuberculosis amongst the staff. (*b*) In the Sanatorium. The staff were provided with complete protective clothing consisting of surgical caps, face masks, surgical gowns, plastic aprons, rubber gloves and rubber shoes. These were supplied for use at all times. Mantoux testing and vaccination were introduced along with mass X-ray.

3. *The Animals.* All sick animals were removed immediately to the Sanatorium. Since the public were excluded from the house the monkeys were encouraged to remain outside.

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Clinical Signs and Diagnosis

Very frequently a tuberculous monkey shows few signs of ill health until quite suddenly, perhaps within 24 hours or less, the animal will become very ill and collapse. This led to difficulty in subsequent treatment. Usually an animal was found to be unable to perch and disinclined to move, and sometimes it would be in a moribund state although it had appeared quite normal on the previous day. There would be rapid loss of appetite and loss in body weight, with or without bowel symptoms. Only on rare occasions was there any coughing. Diagnosis was made on these signs. It is impracticable to take the temperature of monkeys as a routine. The fæces of all suspects were examined regularly, but direct smears are notably unreliable. There was insufficient time or staff available to enable the usual tests to be carried out.

Seventy-three animals were admitted to the Sanatorium. Eighteen did not receive treatment because they died almost immediately, or within seven days. They are discounted in the final analysis. Ten monkeys died during the following two weeks, but are included in the analysis. At the beginning of February, 1955, out of the total, 29 had survived whilst 24 had succumbed. At that time any sick ape excreting acid-fast bacilli in the fæces was considered suspect.

Treatment

On Admission.

(*a*) Moribund animals were kept in an inside cage in the Sanatorium. They were bedded on clean straw under infra-red low-potency irradiation and spoon-fed with brandy and milk. Restorative injections such as camphor in oil, or other cardiac stimulants, were given. Antibiotics were employed also. Laryngeal swabs were taken. This kind of treatment was continued until the patient was capable of sitting up and taking food and liquid voluntarily.

(*b*) When partial recovery had occurred, open-air treatment was introduced. All the less serious cases were given open-air treatment. The patients were transferred to a cage in a den exposed to the fresh air with no warmth and with the den doors open 24 hours per day. A deep hay bed was provided, but there was no other protection. At a later date all cages were placed on trestles in the open air inside a very large cage of chain-link and girder construction, with a tarpaulin roof. As winter approached the sides and ends were covered, but still no artificial heat was provided. As the weather became still more severe the cages were arranged around the sides of loose boxes where the doors were left open all day and closed only at night. This action was taken because it was discovered that the bitter nights of exposure, resulting in a lowering of condition, would threaten to "set back" the improved condition of the animal secured by the previous regimen.

Chemotherapy.

The administration of chemotherapeutic agents was determined by the ability of the animal to accept treatment. The drugs of choice were I.N.H. and P.A.S.—the former was administered in the food or drinking water at the rate

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of 12 mg. per lb. or 5.4 mg. per kilo, the latter at approximately 1 drachm per 14 lb. body weight or 0.6 gm. per kilo. It is understood that the dose for humans of I.N.H. is in the region of 3 mg. per lb. body weight. The justification for the increase to 12 mg. is the clinical observation of the rapidity of increase of activity and spirits which was observed when the dose was increased from 3 mg. to 12 mg. per lb. Even these large doses were not limited by toxic symptoms, but by convenience of dosage.

It is possible that even quicker results might have been obtained if the regular use of streptomycin had been possible, but the disadvantage to the patient of constant restraint with the fear and shock associated with any repeated injection outweighed, in my opinion, the advantages which might have accrued.

Feeding.

The administration *ad lib.* of milk casein to assure a high protein diet was continued for a minimum period of three months, but frequently enormous improvement was observed within the first four to six weeks. Quite often, by the end of two months, the animals appeared perfectly fit and normal, but treatment was continued for a total of three months in all cases. Individual preferences in diet were noted carefully and acted upon.

Clinical Notes.

Method of administration. The I.N.H. was supplied in tablet form, each tablet containing 50 mg. These were crushed and given either in the drinking water or sprinkled on the food. The dose was in two parts, one morning and one evening. When administered in the drinking water the dose was placed in a minimal quantity of water. Until all the water was finished no further fluid was allowed. When the dose was given in the food it was inserted into a section of orange. This segment was fed before the bi-daily feed so that the patient, being hungry, immediately accepted the loaded orange. P.A.S. was used as coated granules, since some difficulty had been experienced in gaining acceptance of the plain powder owing to its unpleasant taste: this was found to be the case also with the compound tablets of I.N.H./P.A.S. The P.A.S. powder adhered to wet surfaces such as cut orange or boiled potato and extra dosage was included to allow for wastage. The degree of wastage was very small since the monkey would always clean up excess granules when all other food had disappeared.

The Future of Animals that Recover

It is important at this stage to stress the fact that I make no claim to have cured monkeys of tuberculosis, but I hope to submit evidence that we have succeeded in arresting the disease. My definition of "recovery" or "cure" is, on the one hand, a monkey who survives the prescribed length of time which various workers have laid down from the day of his infection—a few months at most—and, on the other hand, a monkey who from being critically ill achieves the clinical picture of a healthy animal. A "recovered" monkey should not excrete tubercle bacilli. This important point should be investigated by repeated bacteriological tests wherever possible. Those monkeys which were ill and have

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survived with treatment and are now well must be considered to be recoveries or at least that the progress of their disease has been slowed down. It might be assumed that such monkeys which still survive have some degree of immunity to tuberculous infection since the majority of these animals have not received treatment since recovery and in the main have maintained good clinical health. In some circumstances it is sound policy to destroy an infected monkey forthwith. Those concerned in the administration of a zoological collection have a duty not only to the animals which have been made captive, but also to keepers and public who must be protected from any risk of infection, however slight; therefore any animal noted to be actively tuberculous must be destroyed. There are occasions, however, when treatment in hospital of a rare species is indicated.

Proposed Future Programme.

We are aware that tuberculosis is an ever-present scourge among many of the species exhibited. We should be guided by three criteria in meeting this danger:—

1. No effort should be spared to maintain the health of the animal population by diet or suitable housing.

2. The tuberculous animal should be treated when practicable or otherwise destroyed.

3. An effective programme of preventive medicine including testing and vaccination should be undertaken.

Tuberculin Testing

Tuberculin testing is acknowledged to be of value in laboratory Primates, especially in Rhesus. When confronted with a severe outbreak in 1954, such tests were applied to a much wider range of affected Primates. Our experience does not support the thesis that the tests hitherto elaborated and described are of general application. I propose, therefore, to review work done in the past year in this field.

It is known that Primates will react to tuberculin. Thus it would appear that we have an immediate aid to the detection of the early infection either in the new arrival or in the newly sick. The customary method for the tuberculin testing of monkeys lies in the intra-palpebral injection of 1/10 c.c. of 1 in 100 Old Tuberculin. I am deeply grateful to Dr. Irvine for his advice and help in undertaking this part of the work. Several pilot tests were carried out on groups of monkeys.

(*a*) One group of five monkeys were injected in the upper eyelids, the skin of the forearm, and the skin of the thigh. In the eyelid and forearm sites 0.1 c.c. of 1 in 100 Old Tuberculin was used: in the thigh P.P.D. was used, employing the Heaf multiple puncture technique. These five monkeys were known, clinically, to have had tuberculosis. Four showed no reaction to the test at the third or any other day. One animal, a lion-tailed macaque, showed an œdematous swelling of the upper eyelid but no reaction on the arm or the thigh. He was sacrificed and examination post-mortem revealed old lesions of tuberculosis

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which indicated that he had had the disease, and that it had been arrested. It was not possible to sacrifice the other animals.

(*b*) It was then suggested that B.C.G. test might be employed. This was to consist of the intracutaneous inoculation in the skin of the forearm of 1/10 of a c.c. of 0.75 mg. per c.c. of B.C.G. On the opposing forearm a simultaneous injection of Old Tuberculin was made. These tests were done on a shaved area which was cleaned with ether. A second group of 18 monkeys, clinically "recovered" tuberculous cases, were subjected to this technique. No monkey gave a positive result when injected with Old Tuberculin, but all showed the commencement of a local papular swelling from the third day onwards following the injection of B.C.G. It was noted that the majority at a period between the 7th and 10th days showed, on the B.C.G. site, a pinpoint breakdown at the centre of the swelling.

(*c*) As a control a third group of six presumed tubercle-free animals were injected similarly. The tuberculin test gave a negative reading at the third day: the B.C.G. site did not show swelling or induration until the 8th to 14th days. Perhaps this B.C.G. test may prove of use as an early diagnostic aid. It is easier to inject an animal in the forearm than in the eyelid.

Summary of Findings.

None of these monkeys was a typical laboratory animal such as Rhesus, Mona or African Green, and in view of the divergences of these findings from those hitherto published it is probable that the tuberculin test as hitherto described and carried out is not universally applicable to all Primates as a diagnostic weapon.

Preventive Vaccination

As Livingstone says, "we all admit that preventive medicine does far more in the eradication of tuberculosis than the puny efforts of the clinician in dealing with the sick." It would be comforting to think that vaccination of all the Primates coming into captivity using either B.C.G. or Vole vaccine would ensure their subsequent freedom from tuberculosis. In the Zoological Gardens and in the presence of a constant infection, immunisation of the new arrival would be highly desirable. Dr. Irvine and Dr. Wells suggested to me that the subcutaneous injection of 40 mg. of B.C.G. into presumed tubercle-free animals might prove advantageous. Some of the debatable factors involved are as follows:—

1. The uncertainty of the literature as to precise dosage.
2. The uncertainty as to conversion time.
3. The uncertainty as to size and species variation.
4. The disfigurement which might result from local scarring.
5. The risk of secondary infection at the vaccination site due to unhygienic habits.
6. The differing opinions held as to the duration of any immunity produced.
7. The species variation of tuberculin tests used to determine the conversion.

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Technique.

The animal is anæsthetised with nitrous oxide. An area just below the left shoulder blade and lateral to the spine is shaved and disinfected with ether. The inoculum is introduced subcutaneously in the usual way.

Clinical Course.

Reaction to the vaccination occurs approximately seven days afterwards, when a discrete swelling appears in nearly all cases. Induration appears about the 14th day and finally a pinpoint breakdown occurs, usually with discharge of pus. Providing the lesion is not interfered with by the animal—and at no time does he appear to be in pain—from the 21st day onwards the discharge of pus ceases and is replaced by serum. There is then a gradual recession of the induration: meanwhile the animal remains in perfect health.

Conclusion

It has been established that it is feasible to vaccinate Primates against tuberculosis. It remains to establish by clinical experience that any immunity conferred persists under the everyday conditions of a zoological collection. The maintenance of this immunity must be controlled by a reliable test. We have reason to hope that B.C.G. vaccine applied to the forearm may give suitable control. Such a test is an indispensable part of any programme aiming at the eradication of tuberculosis in Primates in captivity by preventive vaccination.

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PREVALENT DISEASES OF POULTRY IN EGYPT

By ZAKI MORCOS, F.R.C.V.S., M.V.Sc., D.V.H.(Eng.)

THE following are serious and prevalent diseases in poultry in Egypt.

I. *Fowl Plague.*

Fowl plague and Newcastle disease are two distinct diseases. Fowl plague attacks all breeds of fowls of all ages and the death rate is high. The acute form does not allow time for symptoms to show; when subacute, fowl plague has outstanding signs, œdema of the head and joints together with venous hyperæmia as well as unfeathered areas. The incubation period is 1 to 5 days, the course 1 to 6 days, and the mortality may be over 90 per cent.

Immunisation may be by a virus passed into pigeons and then to the chick embryo when it becomes fixed. Virus has been passed by the author intracranially into white mice; after a preliminary incubation of seven days it is fixed after the fifth passage to three days. This killed normal fowls after six days instead of an average of three. Dryness did not aid attenuation but ether was added in 1 per cent to the neurotropic fixed virus and this proved an excellent vaccine.

II. *Newcastle disease.*

During late years both fowl cholera and fowl plague have been rare in Egypt, whereas Newcastle disease is prevalent. There is a longer period of incubation in comparison with fowl plague and there are bronchial and nervous symptoms. Mortality is very high. Immunisation is by an attenuated virus passaged through chick embryo; it is a reliable vaccine and safe when used in sub-doses.

III. *Fowl spirochætosis and Piroplasmosis.*

These are both carried by the same tick (Argasidæ) and both infections are among the most serious obstacle in rearing European breeds in Egypt. Vectors become resistant to insecticides and this makes it inevitable for Egypt to concentrate on cross breeding, selection and cultivation of its own heat and disease-resistant breeds.

Spirochætosis and piroplasmosis are characterised by the gradual emaciation of the bird until on handling it feels like a skeleton studded with feathers.

Prevention: Unfortunately ticks become resistant to insecticides and both larvæ and adults carry the infection. Ducks act as reservoirs and must be reared and kept separate from fowls.

Treatment: Atoxyl is superior to all other arsenical preparations in spirochætosis; to this is added 0.1 per cent trypan blue or piro blue. A dose of 0.5 to 3 ml. is given intramuscularly on three successive days according to the age and size of the bird. Other arsenicals and antibiotic preparations are not to be compared with Atoxyl.

IV. *Pullorum disease.*

The cultivation of *blood clot* is a reliable method of diagnosis; whole blood is not as successful possibly due to antibodies in the serum.

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Prevention is by three daily doses of 250 mg. per mouth of Terramycin for adult hens and chicks.

Eggs laid on the seventh day of treatment are free from *Sal. pullorum* and the blood clot is negative on fifth day of treatment.

V. *Tuberculosis.*

This is usually generalised in fowls. The abdominal cavity may be full of nodules, some calcified, some gritty, and some purulent, varying in size from 0.25 to 1 cm. Pus may contain acid fast bacilli.

Prevention: The only reliable line to adopt is the destruction of the reactors to tuberculin together with rigid hygienic precautions.

VI. *Fowl pox.*

These lesions, whether round the face, over the body, or on mucous surfaces forming false membranes, dry on saturation with iodine solution (without glycerine, which preserves the virus), or with a strong watery solution of pot. permanganate; the latter must not be allowed to be swallowed by the bird as it is highly toxic.

Prevention: Intradermal inoculation of emulsion of pigeon pox lesions.

VII. *Pigeon Salmonella* (Pigeon Paratyphoid).

This is a slow, progressive septicæmia caused by a gram negative organism. The birds become weak, lazy, waste away, and discharge an intense green diarrhœa; homers become unable to fly any distance. Fowls and sparrows are resistant; rabbits, rats and mice are susceptible on artificial inoculation, while guinea pigs are refractory.

VIII. *Coccidiosis.*

This disease attacks birds over three weeks old. Diagnosis is by microscopic examination and sulphamezathine is so far the best treatment, together with good hygiene.

HÆMOLYTIC *BACT. COLI* IN THE "BOWEL ŒDEMA" SYNDROME

Part II—Transmission and Protection Experiments

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Introduction

A CONDITION which is indistinguishable from "œdema disease," as far as symptoms and post-mortem lesions are concerned, may be produced in healthy pigs by injecting them intravenously with a preparation from the contents of small intestine of pigs which have died from the disease. Timoney (1950) first demonstrated this, and it has been repeated by Lamont *et al.* (1950) and Hudson, Huck and Shand (1951). Schofield (1955), on the other hand, was unable to confirm this observation.

Allied to this observation, Hudson, Huck and Shand maintain that hæmolytic *Bact. coli* are constantly present in the intestines and sometimes in the mesenteric lymph nodes of pigs dying from œdema disease.

This finding has been recorded also by Schofield, and we have repeatedly isolated a similar organism in cases examined at Weybridge. Whilst hæmolytic coliforms commonly occur in pigs suffering from a variety of conditions and also in healthy pigs, the fact that this organism is constantly present in cases of œdema disease and that it is recoverable in pure or nearly pure culture, suggest that it might be involved in œdema disease.

On the basis of this it was decided to use this organism, and to attempt active and passive protection of pigs against the effects of the extracts capable of reproducing the experimental "bowel œdema" syndrome.

Outbreak from which the Material was Obtained

Ref: 1/9/F.

The outbreak involved piglets which were weaned on August 24, 1955, having been farrowed between August 7 and 11 from several gilts. The first sign of disease was on August 31, when the first piglet died. Several died on September 1, and the symptoms described by the owner were consistent with "œdema disease," namely, staggering and puffiness of the eyelids. The piglets had been weaned on to a proprietary sow milk substitute and appeared to be thriving fairly well.

Post-mortem Examination

Six piglets were examined, and the following was noted: Fine fibrin shreds lying on the viscera in several of the carcases; considerable thickness of facial œdema in one only; œdema in the sub-peritoneal tissue between the kidneys in two; the mesenteric lymph nodes slightly enlarged and congested; carcase lymph nodes showed slight congestion in most of the cases; no other lesions.

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On September 3 two more carcases from the same batch of pigs were received; one was a runt and showed marked œdema over the nasal bones, the other showed slight œdema in a small area of the gastric submucosa.

Hæomlytic *Bact. coli* were recovered in almost pure culture from the intestinal contents of these two pigs.

Preparation of the Material

The small intestinal contents of six of the piglets were pooled and were about 300 to 400 c.c. in amount; 200 c.c. saline were added, and the mixture shaken and left to stand overnight at room temperature. The following day it was centrifuged at 3,000 r.p.m. for 30 minutes and the turbid brown supernatant fluid was collected and stored at —20° C.

Activity of Extract

On September 6, 1955, 15 c.c. of the "extract" were administered intravenously to an 8 to 9 weeks old pig (No. 2024) which weighed approximately 35 lb. The animal died 17 hours later and examination post-mortem revealed: gross œdema of the mesocolon; fibrin shreds on the viscera; marked œdema of the greater curvature of the stomach; considerable quantity of peritoneal fluid; œdema of the larynx; excess pericardial fluid and enlarged and congested mesenteric lymph nodes. The appearance was that of a typical field case of "Œdema disease." On bacteriological examination no evidence of hæmolytic *Bact. coli* was found in the intestinal tract and no growth was obtained from the internal organs.

The extract used in this case was not bacteriologically sterile.

Further Treatment of Extract

Having established the potency of the extract, it was centrifuged at 12,000 r.p.m. for 30 minutes, the supernatant was drawn off carefully, dispensed into sterile bottles and stored at —20° C. Bacteriological examination of this supernatant fluid showed a slight contamination in the form of a few hæmolytic colonies of *Bact. coli*.

Next day, September 7, 1955, the extract was removed from the deep-freeze, brought to 37° C., and 14 c.c. of it was injected intravenously into pig No. 2189, which weighed about 50 lb. On the following day the pig was obviously dull. On September 9 the eyelids were swollen, the animal staggered, later on it went down and eventually could support itself on its front legs only. Death occurred on the same day under anæsthesia induced by pentobarbitonium sodium when an attempt was made to collect a blood sample from the anterior vena cava. Examination post-mortem revealed marked subcutaneous œdema over the frontal bones, in the inguinal region and of the eyelids. Œdema of the larynx, stomach wall and mesocolon were also present. The stomach was full; hydropericardium and slight ascites were noted. On bacteriological examination, non-hæmolytic *Bact. coli* and α hæm. streptococci (probably enterococci) were

recovered from the intestine. No growth was obtained from the liver, lung, spleen and kidney.

Another pig, No. 2167, weighing about 60 lb., was given 15 c.c. of the extract intravenously at 10 a.m. on September 9, 1955. At 5.30 p.m. on the same day the animal was unsteady on its legs and refused the evening meal, while other pigs in the same pen ate all the food. Next day the pig was still "off food" but apart from slight puffiness of the eyelids, no abnormality was noted. No change was observed throughout the following day, until suddenly between 6 and 7 p.m. the pig went down, and when urged to get up went into a fit, pedalling violently with the front legs and squeaking in a very hoarse manner. On the morning of September 12 the pig was found dead. Examination post-mortem revealed similar lesions to those in pig No. 2189. In addition there was also marked interlobular pulmonary œdema and œdema of the following sites: along the coronary groove, the gastro-hepatic, mesenteric and mediastinal lymph nodes and the rectus abdominis and psoas muscles. On bacteriological examination non-hæmolytic *Bact. coli* were isolated from the intestine and no growth was obtained from the liver, lung, kidney and spleen.

Attempts at Serial Transmission of the Experimental Bowel Œdema Syndrome

Another transmission experiment was made with an extract of intestinal contents obtained from another field outbreak of "Bowel œdema." The extract was prepared in the same way as 1/9/F and 15 c.c. were given intravenously to pig No. 1841. Throughout the next day the pig was quite normal but on the following morning its eyelids were swollen and by the evening the animal was very dull; the appetite was fairly good. Next day the animal was recumbent, panting and sweating profusely. It was found dead in the afternoon, i.e., within 72 hours of the injection. On post-mortem examination characteristic lesions of the "Bowel œdema" syndrome were noted. On bacteriological examination no growth was obtained from the liver, lungs, kidney and spleen while the intestinal tract yielded the normal bacterial flora. Hæmolytic *Bact. coli* was absent. An extract of intestinal contents of pig No. 1841 was prepared and 15 c.c. injected intravenously into a 10-week-old pig. The inoculum had no effect on the animal which was kept under observation for about two weeks and remained perfectly healthy.

Pig No. 1853 received intravenously 15 c.c. of extract of intestinal contents from pig No. 1841 and 10 c.c. of a six-hour peptone broth culture of strain D (see below). Apart from a transient dullness and lack of appetite on the following morning, no ill-effects were observed.

Isolation of a Further Strain of Hæmolytic Bact. Coli

Another strain (D) of hæmolytic *Bact. coli* was recovered from the small intestine of a pig which died in a further outbreak of "Bowel œdema" and this was similar in cultural characteristics and morphology to strains A, B and C described in Part I. Its biochemical reactions are outlined in the accom-

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panying table and it will be noted that the biochemical reactions of strain D resemble to some extent those of strain B which was also recovered from the intestinal tract.

It was decided to inoculate mice and attempt protection experiments by employing the recovered strain D.

	Litmus Milk	Indol Production	Reduction of Nitrates	Methyl Red	Voges-Proskauer	Citrate Utilisation	Adonite	Arabinose	Dextrin	Dulcite	Galactose	Glucose	Glycerol	Inosite	Inulin	Lactose	Lævulose	Maltose	Mannite	Mannose	Raffinose	Rhamnose	Salicin	Sorbite	Sucrose	Trehalose	Xylose
Strain "A"	A	+	+	+	-	-	AG	AG	AG	NC	AG	AG	AG	NC	NC	AG	AG	AG	AG	AG	NC	AG	AG	AG	NC	AG	AG
Strain "B"	A	+	+	+	-	-	NC	AG	AG	NC	AG	AG	AG	NC	NC	AG	AG	AG	AG	AG	NC	AG	NC	AG	NC	AG	AG
Strain "C"	A	+	+	+	-	-	AG	AG	AG	NC	AG	AG	AG	NC	NC	AG	AG	AG	AG	AG	NC	AG	AG	AG	NC	AG	AG
Strain "D"	A	+	+	+	-	-	NC	AG	AG	AG	AG	AG	AG	NC	NC	AG	AG	AG	AG	AG	AG	AG	NC	AG	AG	AG	AG

+ positive — negative AG — Acid and Gas NC — No Change A — Acid

Mice Inoculations. No attempt was made to find the M.L.D. for mice but 0.4 c.c. of six-hour peptone broth culture proved to be a suitable dose for intraperitoneal and intravenous injections. The latter route was almost invariably fatal, the intraperitoneal on some occasions, with the death taking place within 18 to 48 hours. No nervous symptoms were noted. On examination post-mortem generalised congestion of the internal organs and enlargement of spleen were always present; in some cases following intravenous injections the urinary bladder was found distended with blood-stained urine. Hæmolytic *Bact. coli* was recovered always from the internal organs of dead mice. Subcutaneous injections of a six-hour culture in doses of 0.7 and 0.8 c.c. were harmless to the mice. Control mice given intravenous and intraperitoneal injections of a non-hæmolytic strain of *Bact. coli* from a rectal swab of a pig not suffering from an enteric infection remained healthy.

Mice which survived subcutaneous and intraperitoneal injections were given, four weeks later, intravenous and intraperitoneal injections of 0.4 c.c. of a six-hour broth culture of strain D and they remained unaffected; control mice were injected intravenously and intraperitoneally with the same quantities of the same culture and they died within 24 hours. Post-mortem and bacteriological examinations of the mice which died revealed generalised congestion and hæmolytic *Bact. coli* were isolated from all internal organs.

Production of Hyper-immune Serum

The serum was obtained by intravenous injections of a 10-week-old pig No. 1565 (1934) with six-hour peptone broth culture of strain D; the pig received 10 intravenous injections within $5\frac{1}{2}$ weeks in doses increasing from 10 to 60 c.c. The pig was bled nine days after the last injection. The serum obtained

agglutinated rapidly, on a slide, a saline suspension of strain D, but did not agglutinate 25 strains of *Bact. coli* isolated from pigs suffering from conditions other than "Bowel œdema." By then strains A, B and C were lost. A tube agglutination test was carried out by W. Sojka, M.R.C.V.S., from the Poultry Department at Weybridge and a titre of over 1 : 1,000 was obtained against the somatic antigen of strain D.

Attempts at Passive Immunisation

First Experiment, 12.9.55. Three pigs were used. Each weighed about 50 lb.

Pig No. 2183 received subcutaneously 20 c.c. of the hyperimmune serum.

Pig. No. 1925, subcutaneously 20 c.c. of serum from an apparently normal pig.

Pig. No. 1918 did not receive any serum.

Four to five hours after serum injections all pigs received intravenously 15 c.c. of extract 1/9/F. Next day all three pigs were very dull. The two pigs which received serum looked worse than the control; they both preferred to lie down. Pig No. 1925 (normal serum) refused the food in the afternoon and in the evening would not get up, although it tried to. Its voice was hoarse and the eyelids were swollen. The other two pigs looked slightly better and ate all the food. On September 14 the condition of all the pigs deteriorated and all refused food. Marked dyspnœa was noted in pig No. 1925 (normal serum); it made no attempts to get up even when urged to and in the evening it was lying on its side. Pig No. 2183 (H.I. serum) could stagger about but preferred to lie down. In the evening it could not get up.

The control pig (No. 1918) behaved in almost the same way as No. 2183 but it could still get up in the evening. On the morning of September 15 all three pigs were found dead.

The post-mortem findings in all three cases were as follows:—Marked subcutaneous œdema of the auriculæ (pinnæ) of the external ears and over the frontal bones, ascites, œdema of the larynx, stomach wall, mesocolon and the gall bladder; the gastro-hepatic and mesenteric lymph nodes enlarged and œdematous. In addition the superficial inguinal lymph nodes of pig No. 1918 (control) were found to be enlarged and œdematous.

The experiment was repeated on October 17 and two pigs weighing about 50 lb. each were used. Pig No. P.147 was used as a control and received no serum. Pig No. 146 was given 40 c.c. of the hyperimmune serum subcutaneously and 24 hours later both pigs received intravenously 15 c.c. of extract 1/9/F. On October 19, i.e., the day following injections of the extract, both pigs were quite normal, although towards the evening they were dull and beginning to stagger. On October 20 pig No. P.146 was unable to get up and there was a marked alteration in the tone of its voice. Late in the evening it was lying on its side. It was comatose in the morning of October 21 and died between 1 and 2 p.m. The control pig (No. P.147) staggered very badly in the morning of October 20 and was recumbent in the evening. Next morning it was in fits,

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pedalling vigorously with the fore limbs. The animal was comatose at the time of death of its companion and it was destroyed about half an hour later. The characteristic post-mortem findings of "Bowel œdema" were noted in both cases. The stomach wall was œdematous and about one inch thick in both cases. There was excess of fluid with jelly-like particles in the pericardial sacs of both pigs. The liver, lungs, kidneys and spleen were bacteriologically sterile and only non-hæmolytic *Bact. coli* were found in the intestinal tract.

An Attempt at Active Immunisation

A 50 lb. pig, No. 2458, received, within 10 days, three intravenous injections of 6½-hour peptone broth culture of strain D. The doses were 14, 16 and 20 c.c.

Blood samples were taken from the anterior vena cava immediately before and five days after, the last injection. On tube agglutination test against the somatic antigen of strain D the titre of the first sample was 1 : 800 and that of the second sample between 1 : 800 and 1 : 1,600. On slide test the serum rapidly agglutinated a saline suspension of strain D but failed to agglutinate 25 strains of hæmolytic and non-hæmolytic *Bact. coli* isolated from pigs suffering from conditions other than "Bowel œdema."

Five days after the last injection of culture the pig received 15 c.c. of extract 1/9/F intravenously. On the following day the animal was staggering on its hind legs but its appetite was still good. Within the next two days the pig's condition gradually deteriorated and on the fourth day it was found comatose and on its side. Just before death a blood sample was taken from the anterior vena cava and a titre of 1 : 800 was obtained against the somatic antigen of strain D. Post-mortem examination revealed œdema of the eyelids, stomach wall, larynx, mesocolon and renal pelvis; ascites with jelly-like particles and hydropericardium. On bacteriological examination non-hæmolytic *Bact. coli* and hæmolytic streptococci (probably enterococci) were isolated from the intestine. No growth was obtained from the liver, lungs, kidney and spleen.

A small-scale protection experiment was also made with mice along the lines usually employed for typing toxins. The 1/9/F extract was passed through a Zeitz sterilising pad and on subsequent bacteriological examination was found to be bacteria-free. Nine mice in groups of three were used. The first group received 0.4 c.c. of the bacteria-free filtrate, the second group 0.4 c.c. of a mixture consisting of 0.4 c.c. of filtrate and 0.2 c.c. of normal saline; the third group 0.4 c.c. of mixture of 0.4 c.c. of filtrate and 0.2 c.c. of serum from pig No. 1565. All injections were made intravenously and all the mice were found dead within 48 hours. No macroscopical lesions were seen on examination post-mortem and bacteriological examination proved negative. Three groups of three mice injected intravenously with bacteria-free filtrates of intestinal contents collected from pigs not suffering from "Bowel œdema" remained apparently healthy.

Discussion and Conclusions

Timoney (1950) and Schofield (1954) both suggested that "Bowel œdema" may be a specific toxæmia. Schofield maintained "that the history of outbreaks,

symptoms and lesions all strongly suggest a primary enterotoxæmia, the œdema being one manifestation of the toxæmia." In 1955 he referred to a relationship between the disease and hæmolytic *Bact. coli* recovered from fæcal cultures of "Bowel œdema" pigs. His attempted immunisation of pigs with a bacterin prepared from hæmolytic *Bact. coli* failed. Our attempt to protect the pigs by either whole live cultures or serum prepared against this culture failed also. The bacteria-free extract of intestinal contents proved fatal to mice on intravenous injections and the mice could not be protected by our serum. It appears that the lethal factor present in the bacteria-free filtrate might well be a toxin and, assuming that our serum contained only antibacterial antibodies and no antitoxins, neutralisation of toxins would not occur. Although the number of animals used was relatively small, our findings are compatible with the enterotoxæma theory and if the relationship of hæmolytic *Bact. coli* with the "Bowel œdema" syndrome is of an obligatory character, and the field evidence so far seems to indicate that it is, then some further investigation on the possibility of toxin production is called for.

Summary

1. Intravenous injections of pigs with extracts of intestinal contents of pigs dying in a field outbreak of "Bowel œdema" constantly reproduced the "Bowel œdema" syndrome with the characteristic clinical symptoms and typical post-mortem findings, but attempts at serial transmissions failed.

2. Attempts to induce active or passive immunity in pigs against this extract by employing either live cultures of a strain of hæmolytic *Bact. coli* recovered from a field outbreak of "Bowel œdema" or immune serum prepared against this strain of *Bact. coli* failed.

3. Bacteria-free filtrate of the "extract" was fatal to mice on intravenous injection and the mice could not be protected with the immune serum used in the above experiment.

4. The hæmolytic *Bact. coli* which were recovered constantly in pure culture from the intestinal tract of pigs dying in field outbreaks of "Bowel œdema" were absent in the experimental pigs.

Acknowledgments

The authors wish to express their gratitude to Dr. A. W. Stableforth for permission to publish this work; to Mr. J. R. Hudson for his encouragement, help and advice; to Mr. A. Shand for his help in preparing this report, and to Mr. W. Sojka for carrying out the serological tests.

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SOME OBSERVATIONS ON THE FŒTAL CIRCULATION IN THE CAMEL

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THE description given in the current text-books, as in Chauveau (1891), Strangeways (1915), Sisson (1940), Barclay, Franklin and Prichard (1944), about the mammalian fœtal circulation is based mainly on the studies made of the dog, horse, ox and pig. Little is known of the fœtal circulation in the camel. In view of the dearth of information regarding this subject the following personal observations may be of some interest.

Ten fœtuses of different dimensions, collected from the Cairo abattoir, were examined. It is difficult to estimate their age in the absence of "age-estimate tables" for camel. Of these fœtuses, five only were dissected while they were fresh, the rest after being injected through the umbilical vein with a solution consisting of formalin, glycerin and wash-blue.

The following are the principal characters which have been noted concerning the fœtal circulation of camel:—

The umbilical cord in the fœtus is comparatively more voluminous than that of the other domesticated animals so far studied. The two umbilical arteries together were of a calibre equal to that of the umbilical vein.

Before injection, the abdominal vein was opened ventrally just behind the umbilicus in order to trace its course. It was found that the vein, covered with a thick layer of peritoneum by which it is attached to the abdominal wall, passes forwards and upwards towards the umbilical fissure of the liver.

The vein undergoes noticeable changes when it penetrates into the liver. Its wall becomes thinner, and it begins to ramify. These ramifications spread all over the liver tissue of the left and middle mass. The portal vein pierces the pancreas and is directed towards the right mass of the liver where it branches into many fine tributaries. In the right mass, the terminal branches of the umbilical vein join the tributaries of the portal vein.

No direct branch from either the portal or the umbilical vein was found uniting with the posterior vena cava. The blood of both veins is carried to the posterior vena cava through the second and fourth hepatic veins. The posteior vena cava passes in a groove on the right border of the liver and in some places it is completely covered with liver tissue.

There is, however, not much difference from the other domesticated animals in the rest of the circulation.

Conclusion

(1) Umbilical vein does not join the portal vein before it enters the liver as is the case with some animals.

(2) Ductus venosus is absent in the fœtuses of the camel.

I wish to express my gratitude to Dr. S. Fouad, Dean of the Faculty of Veterinary Medicine, for his interest in this work. My best thanks are also due to the Director of the Abattoir, Cairo, for the materials, and to Dr. Hegazi of the Anatomy Department for his help in the preparation and dissection.

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"MULBERRY HEART" DISEASE IN PIGS

By J. B. TUTT, M.R.C.V.S., and F. JOHN GALE, B.V.Sc., M.R.C.V.S.

Winchester

THE outbreak of "Mulberry Heart" disease occurred in a herd of pedigree Saddleback pigs. The animals were farrowed in October, 1956, and to date (January 25, 1957) 10 pigs have died. Four litters were involved as follows:—Six pigs from one litter, one pig from one litter, two pigs from one litter, one pig from one litter. The deaths occurred in a batch of 259 pigs housed in five converted railway carriages, with separate restricted outside runs. Five deaths occurred in the first house, three in the second and two in the fifth.

When the pigs were three weeks old, and still on the sow, they were fed on weaner pellets and when they were approximately 6½ to 7 weeks old they were transferred to weaner meal which was given *ad lib.* The formula of the latter is as follows:—Barley meal, 9¾ cwt.; fish meal, 1 cwt.; soya bean meal, 1½ cwt.; dried dist. concentrate, ½ cwt.; wheat meal, 6 cwt.; grass meal, 1 cwt.; limestone flour, ¼ cwt.; Vit. D.3 supplement, 2 lb.; penicillin, 4 lb.; zinc carbonate, ½ lb.—20 cwt. 6½ lb.

The in-pig sows run out at grass and farrow out of doors, and sows and litters remain at pasture for the first eight weeks, or until weaning.

All litters were sired by the same boar and there were no unaccountable deaths in any of the previous litters from the sows.

History

Four pigs were taken ill and died within 12 hours. The signs evinced were heavy respiration, inco-ordination of gait and inappetence. The remaining six pigs became ill suddenly and died within a few days.

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Examinations post-mortem on the farm revealed a pathological picture common to all. There were numerous hæmorrhages in the epicardium and endocardium and an excess of fluid in the pericardial sac. Two pigs showed evidence of a severe gastritis and one of ascites with fibrin formation. No diagnosis was made and when the next three pigs died they were despatched to the Veterinary Investigation Centre at Weybridge. The report on the post-mortem examination was as follows:—

1. Weight 40 lb. Swollen spleen, general wet appearance of carcase; œdema over shoulders, back of neck and up to the base of the ears. The most noticeable post-mortem finding was the presence of numerous hæmorrhages under epicardium and endocardium.

2. Weight 32 lb. Ascites with shreds of fibrin in the abdominal cavity. Excess fluid in the thoracic cavity and pericardial sac; consolidation of apical and cardic lobes of the lungs; again the most prominent features were numerous hæmorrhages under the epicardium and endocardium.

3. Weight 30 lb. Fluid in the thoracic cavity and pericardial sac; serofibrinous pericarditis, numerous hæmorrhages under epicardium and endocardium.

A diagnosis of "Mulberry Heart" disease was made but they were unable to recover any known pathogen at the laboratory.

We were informed also that this condition has been recognised by Professor Lamont in Northern Ireland.

Conclusions

We were not able to attribute the trouble to any particular factor, dietetic or infective. We acknowledge the help and advice given to us by the Investigation Centre at Weybridge and particularly so in the matter of diagnosis.

REVIEWS

MONNIG'S VETERINARY HELMINTHOLOGY AND ENTOMOLOGY, by G. Lapage. London: Baillière, Tindall and Cox. Pp. xv + 511. 4th Edit. 1956. Price 42s. net.

ALTHOUGH there have been changes in the order in which the different sections are presented, this fourth edition, revised by Dr. Lapage, preserves the many valuable features which made the textbook so successful throughout its three earlier editions. A new introductory chapter has been written and the section on technique, which in earlier editions followed the introduction, has now been transferred to near the end of the book. Some additions have been made to this section which also includes Dr. Mönnig's drawings of helminth eggs, now reproduced on art paper. The proximity of this section to the host-parasite list is an improvement. The use of footnote references has been abandoned and these have been collected, together with some others that have been added, as a bibliography immediately preceding the index at the end of the book.

New material includes additions to those parts dealing with the treatment and control of helminths. To a great degree the account of the equine strongyles has been rewritten. The most extensive changes occur in the entomology section in which a new general account of the Arthropoda is given together with a revised classification of the phylum. Readers familiar with the earlier editions of this book will notice that the names of some genera, families, orders and classes, etc., have been changed to conform with modern terminology. Recent work on the use of the newer insecticides and acaricides has also been included. A few new figures and a number of photographs from Thornton's *Textbook of Meat Inspection* have been added. The changes improve the book which will continue to be a useful text for veterinary undergraduates and practitioners.

NEOPLASMS OF THE DOMESTICATED MAMMALS, by E. Cotchin. Commonwealth Agricultural Bureau. Price 20s.

THE study of new growths in the domestic animals may open a door to a better understanding of the ætiology, pathogenesis, prevention and cure of similar lesions in man. Research workers need not fear any shortage of material of both the benign or malignant varieties. Indeed, if there be a shortage it is of manpower for the amount of material which goes to waste daily in the slaughter-houses, knackeries and small animal clinics is colossal. The author of this monograph is one of the few who in modern times has remained faithful to the study of macro and micro morbid anatomy and not been lured away from the very basis of pathology by the more immediate glamour of microbiological and biochemical techniques.

In his most interesting introduction the author gives what is an historical review of past workers and the relevant literature. It is interesting to note that the most important work in the English language dealing with the neoplasms of domesticated animals was published only 25 years ago. In his introduction

he surveys also the general incidence of tumours, their relation to the different species, metastasis and ætiology.

The main text of the monograph is divided into 14 sections or chapters. Each part reviews the incidence of, and the literature relating to, the tumours which affect the various systems and tissues of the body. A great fund of extraordinary information is disclosed. It will be noted that gastric, renal and pancreatic neoplasms are rare, even in the dog. After reading the text one is tempted to ask why should mammary neoplasms of the cat be malignant so frequently; why should the horse and the dog be more liable than other animals to melanotic growths; why should the cat be the only frequent victim of œsophageal carcinoma, and why is the prostate gland the seat of malignant growths so rarely? If one could find a correct answer to these questions, and there are many more that one might pose, the problem of malignancy might be on the way to a solution.

The author has supported his own views and findings with a wealth of material culled from the literature. When one reads the text and notes the bibliographical list it is obvious that his reading must have been extremely wide, arduous and time consuming. He has packed a wealth of information within the covers of a relatively small book and made it interesting. Impelled by the scourge of cancer there are signs of a return to favour of the cult of morbid anatomy. Mr. Cotchin has shown what good trout lie in the stream of comparative pathology, a stream which has been scarcely rippled. They await the anglers who will catch them and weigh them in the balance. Students, graduates and research workers in this realm will welcome this timely, concise and authoritative review.

OBITUARY

Arthur Clifford Attree

It is with great sorrow that we record the passing of Arthur Attree. He died on Sunday, April 28, at his home at Birchington-on-Sea. Mr. Attree was known and respected by many members of the medical and veterinary professions for he was employed in the sales department of Baillière, Tindall & Cox. For many years he attended B.M.A., B.V.A. and other congresses at which he was in charge of the firm's stand in the Exhibition section.

Attree joined Baillière, Tindall & Cox when he was 16 years of age and in the course of passing from office boy to being in charge of the sales and despatch department he became conversant with every facet of the scientific book and publishing trade. There must be few men who can approach the wealth of his knowledge concerning medical and veterinary publications. He was conversant with the old and the new and his memory of authors, dates of publication and costs was remarkable.

He could have retired two years ago but he dearly wanted to serve the firm for 50 years. The vital date was January, 1957. He retired in March to a small house and garden which he had acquired at Birchington-on-Sea. He had not been in his usual good health for about two years but having achieved a cherished ambition of 50 years' service he and his friends hoped that the sea air and the peace of his garden would soon put matters right. This was not to be.

Attree loved his work, he enjoyed his life with the firm, to which he was intensely loyal, and his contacts with his medical and veterinary friends. We shall all miss his vigorous, cheery nature and the ebullience of his native "cockney" wit but one cannot visualise that Attree would have been completely happy away from his books and colleagues and Henrietta Street where he had worked so long and with such loyalty and efficiency.

NOTICES

British Veterinary Surgeon receives U.S.A. Research Centre Trophy

A TROPHY has been presented by the Gaine's Dog Research Centre, New York, to Mr. A. E. Harrop, M.R.C.V.S. Mr. Harrop is a Senior Lecturer in the Department of Animal Husbandry at the Royal Veterinary College, London.

The trophy is a mark of the Research Centre's appreciation of the work which has been done by the recipient on artificial insemination of dogs. It will be recalled that Mr. Harrop published in this journal (*Brit. vet. J.*, 110, 10.1954) the record of the successful artificial insemination of a bitch using preserved semen (100 hours old) and later described the first transatlantic A.I. conception (*Brit. vet. J.*, 112, 8.1956).

Improved Pulpy Kidney Vaccine

EVANS MEDICAL SUPPLIES LTD. announce the introduction of a new product, an Improved Pulpy Kidney Vaccine. This is reported to be a vaccine of considerably increased potency, the recommended dose of 2 ml. resulting in high flock titres and a consequent reduction in the percentage of sheep remaining inadequately protected after injection.

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